REMARKS

In view of at least the Amendment and Supplemental Response, Applicant believes the pending application is in condition for allowance.

Dated: February 8, 2008

Respectfully submitted,

By _____
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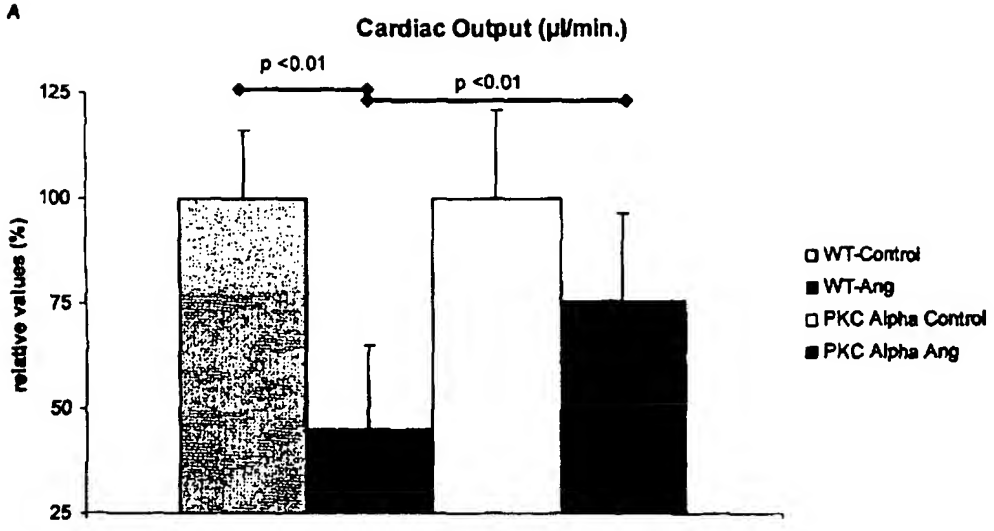
PKC alpha knock-out mice and heart failure

Experiments were performed with male 129/SV PKC alpha knock-out mice and 129/SV wild type (WT) animals from the strain that was used to generate the 129/SV PKC alpha knock-out mice. Animals were kept at 22±2°C and exposed to a 12 h dark/light cycle with free access to standard chow and tap water. All procedures were carried out according to guidelines from the American Physiological Society and were approved by local authorities. 10-14 weeks old mice were used. Osmotic minipumps (Alzet Model 2004, Alza Corp) containing either ANG II (0.15 mg/kg/d) or normal saline were implanted in the mid-scapular region under anesthesia. Angiotensin II was continuously infused for 28 days. The blood pressure was measured by tail cuff plethysmography (TSE, Homburg). A baseline measurement was performed the three following days. The next blood pressure measurements were performed after 28 days. Angiotensin II infusion for 28 days did not lead to an increase in blood pressure nor to an increase in heart rate. The weight of the animals of the different groups did also not differ from each other.

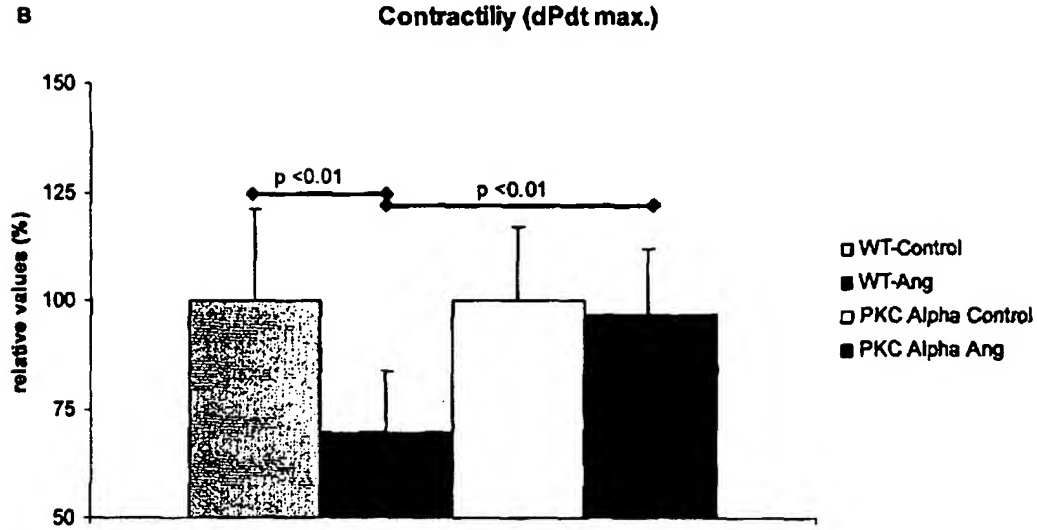
Cardiac contractility

For right ventricular catheterization mice were anesthetized and mechanically ventilated with enflurane (3%), a bilateral vagotomy was performed and 1.4-F micromanometer conductance catheter (SPR-719; Millar Instruments) was positioned in the left ventricle via the right carotid artery. 28 days of ANG II infusion resulted in decreased cardiac output in WT animals compared to those receiving sham infusions. Surprisingly, in KO mice ANG II did not significantly impair cardiac output (Fig. 1A). Cardiac contractility in ANG II treated WT animals was significantly decreased, whereas in ANG II treated KO mice contractility was nearly the same as in untreated WT or KO mice (Fig. 1B). The stroke volume was significantly diminished by ANG II infusion in WT animals and was preserved in KO mice (Fig. 1C).

A


Cardiac Output (µl/min.)
p <0.01
p <0.01
125
100
75
50
25
relative values (%)
WT-Control
WT-Ang
PKC Alpha Control
PKC Alpha Ang

B


Contractiliy (dPdt max.)
150
125
100
75
50
p <0.01
p <0.01
relative values (%)
WT-Control
WT-Ang
PKC Alpha Control
PKC Alpha Ang

C

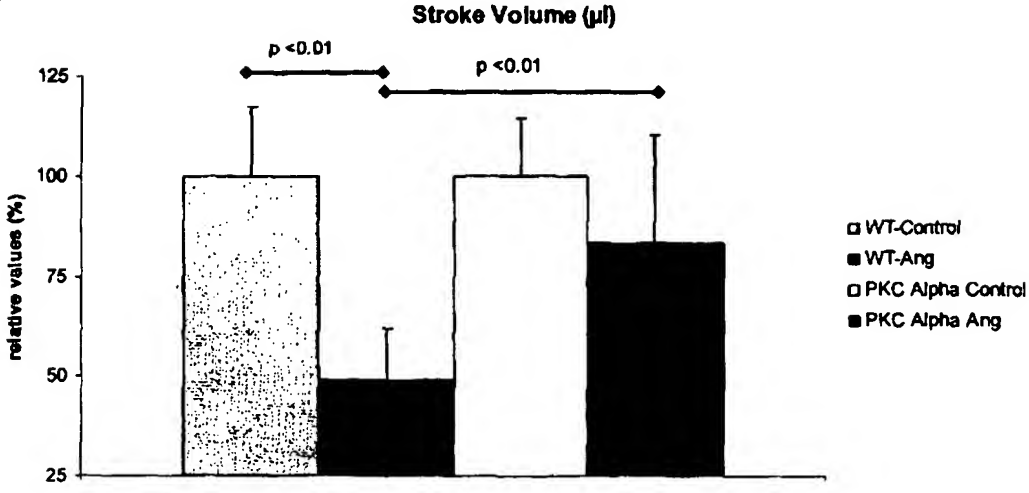

Stroke Volume (µl)
p <0.01
p <0.01
125
100
75
50
25
relative values (%)
WT-Control
WT-Ang
PKC Alpha Control
PKC Alpha Ang

Figure 1: Indices of cardiac function in PKC alpha knock-out (KO) and WT mice treated with subpressor dosages of ANG II. Control mice were treated with sham infusions. Panel A shows the changes in cardiac output. WT animals with ANG II show a reduced cardiac output versus WT control animals (798±156µl versus 1770±128µl, **p<0.01). No significant changes were detected in ANG II treated KO mice compared with KO control mice. Panel B shows the changes in myocardial contractility. ANG II treated WT mice have a reduced cardiac contractility compared to ANG II treated KO mice (6183±554 mmHg/sec. versus 8487±548 mmHg/sec., ## p<0.01) and WT control mice (8871±841 mmHg/sec, *** p<0.001). Panel C shows changes in stroke volume. ANG II in WT leads to a reduced stroke volume (3.84±0.3µl versus 1.88±0.22µl, *** p<0.05).

Cardiac hypertrophy

After sacrifice, the heart was removed from mice and the right ventricle was dissected from the heart. The left ventricle was weighted. As expected ANG II infusion for 28 days lead to a gain in cardiac mass assessed by LV-to-body weight ratio (LV/bw ratio) in WT animals. The cardiac mass was increased by 16% in WT ANG II treated compared to untreated WT mice. Surprisingly, in KO animals LV-to-body weight ratio was not affected by ANG II infusion.

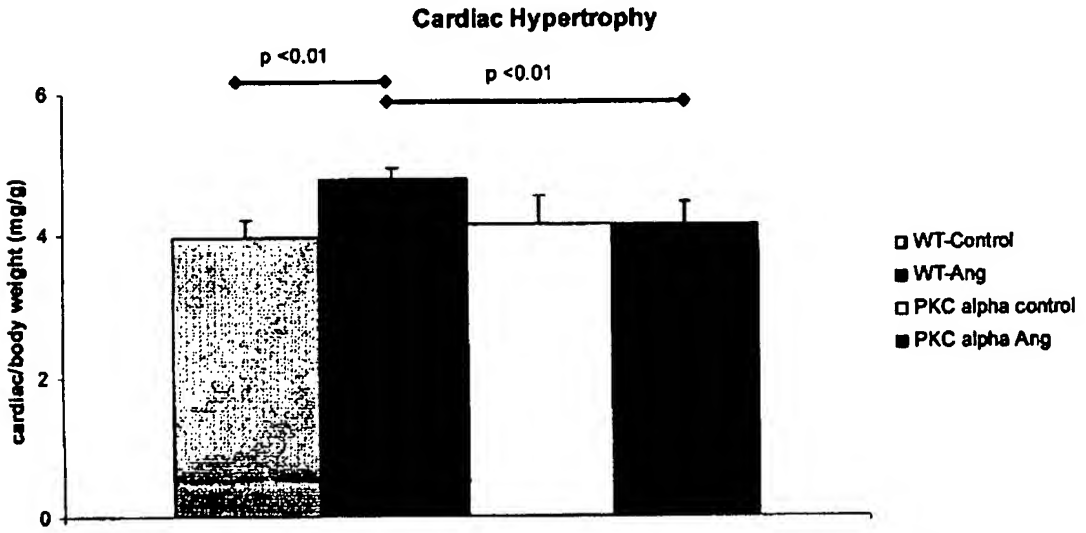


Figure 2: Left ventricular weight/body weight ratio in PKC alpha knock-out (KO) and WT. WT mice treated with ANG II show an increase in left ventricular mass compared with ANG II treated KO animals (4.8±0.07 mg/g versus 4.14±0.14 mg/g, p<0.01) and untreated control WT animals (3.96±0.1 mg/g, p<0.01). There is no change in left ventricular mass between Ang II KO mice and KO control animals.

Immunochemistry

Immunohistochemistry for fibronectin was performed with a rabbit polyclonal anti-fibronectin antibody (catalog no. 14-109-0568; Paesel+Lorei, Frankfurt, Germany). Specimens were analyzed using a Zeiss Axioplan-2 imaging microscope with the digital image-processing program AxioVision 4.3 (Zeiss, Jena, Germany). Both untreated WT and KO mice showed a basal expression of fibronectin mainly in the perivascular field and in the interstitium between myocytes. After ANG II infusion WT mice showed a more prominent staining in the interstitium and an increased staining for fibronectin in the perivascular fields. However, in KO animals treated with ANG II less positive staining for fibronectin could be detected both in the perivascular fields and in the interstitium. The fibronectin expression was semi-quantified by using a scaling scheme ranging from 1-3 where one was related to a weak, 2 to a medium and 3 to a strong expression of fibronectin. The quantification of fibronectin expression showed that the fibronectin production was significantly less in KO animals compared to treated WT animals.

In summary, these data suggest surprisingly, that PKC alpha is an important mediator of cardiac contractility and left ventricular hypertrophy.

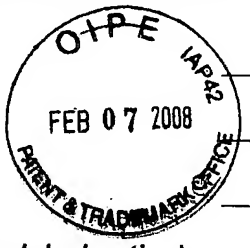
144737
Venable Filing Number

PATENT PROSECUTION RECEIPT OF FILING

COPY

Attorney/LAA: MEK/ftp
PTO Due Date: February 7, 2008
Atty. Docket No: 37998-237159
Current Date: February 7, 2008
Title of Application: INHIBITION OF PROTEIN KINASE C ALPHA FOR THE TREATMENT OF CARDIOVASCULAR DISEASES
Application No: 10/528,806
Filing Date: June 14, 2005
Patent No. :
Issue Date:

The following items were received from Venable LLP, Washington, D.C., by the U.S. Patent & Trademark Office on the date stamped hereon:



		U.S. PTO FEES ENCLOSED	
x	**Transmittal Letter**		Filing Fee
x	**Fee Transmittal Letter**		Search Fee
	New U.S. Patent Application		
	(____ pages of specification/claims)		Examination Fee
	Rule 53(d) Continued Prosecution Application		
	Rule 53(b) Continuation or Divisional Application		Additional Claim Fee
	(attach copy of specification, claims, drawings and declaration)		
	U.S. National Stage Application of PCT Application		
	Request for Continued Examination (RCE) under 37 CFR 1.114	1,050.00	**Extension Fee**
	Application Data Sheet		
	Substitute Specification		IDS Fee
	Priority Document-Cert. Copy of Appln.#:_____; Country: _____; Date Filed: _____		Recordation Fee
	Formal Drawings (___ sheets, Figs.)		
	Inventor Declaration		Notice of Appeal Fee
	Assignment w/Cover Sheet		
	Response to Notice to File Missing Parts		Brief on Appeal
	Response to Notice to File Missing Requirements		
	Response to Requirement		Oral Hearing Request Fee
	Information Disclosure Statement with cited references		
	Response		Petition Fee
x	**Amendment (including Appendix A)**		
x	**Petition/Request for Extension of Time (3 mo. ext.)**		Issue Fee
	Power of Attorney		
	Petition to Revive		Publication Fee
	Sequence Listing – CDR Enclosed? __ Yes __ No		
	Request for Non-Publication		Certificate of Correction Fee
	Request to Rescind Non-Publication Request		
	Terminal Disclaimer		Maintenance Fee
	Notice of Appeal		
	Appeal Brief ***(in triplicate)*** / Reply Brief ***(in triplicate)***		Other Fees (Describe)
	Request for Oral Hearing		
	Confirmation of Hearing Petition		
	Issue Fee Transmittal		
	Certificate of Correction	1,050.00	**Total Fees Paid**
	Maintenance Fee Transmittal		
	Status Inquiry		**Charge the above fees as follows:**
	Other: (*Please describe below*)		
		x	**USPTO Deposit Account No. 22-0261**
		☐	**USPTO Deposit Account No.** _____
		☐	**USPTO not to charge any Deposit Account**

Reviewed By: Walter L. Kelley
Signature of Attorney

2/7/08
Date

LAH

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Meene et al.

Art Unit: 1644

Application No: 10/528,806

Examiner: S. X. Wen

Confirmation No: 6218

Filed: June 14, 2005

Atty. Docket No: 37998-237159

For: INHIBITION OF PROTEIN KINASE C ALPHA FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

Customer No:
26694
PATENT TRADEMARK OFFICE

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated August 7, 2007, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 9 of this paper.

AMENDMENTS TO THE SPECIFICATION

In response to the Examiner's request, please amend the first line of the specification to add the following:

> This application is a national stage entry of International Application PCT/DE2003/003165, which was filed September 23, 2003 and claims priority to DE 102 44 453.6, which was filed September 24, 2002.

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of treatment and/or prevention of cardiovascular diseases in patients comprising administering an effective amount of at least one ~~agent~~ inhibitor ~~of PKC which reduces or inhibits the expression and/or activity~~ of protein kinase C-α (PKC-α).

2. (previously presented) The method of claim 1, wherein said cardiovascular diseases which affect the filing state and tonus of the circulatory system and the output performance of the heart are selected from the group consisting of coronary heart disease, myocardial infarction and stroke.

3-8. (cancelled).

9. (previously presented) The method of claim 1, wherein said agent is selected from the group consisting of at least one nucleic acid which reduces or inhibits the expression of the protein kinase C-α gene, a vector containing said nucleic acid, a host cell containing said vector, a substance which reduces or inhibits the expression of protein kinase C-α, a substance which inhibits the translocation of protein kinase C-α, an antagonist of protein kinase C-α activity, and an inhibitor of protein kinase C-α activity.

10. (withdrawn) The method of claim 9, wherein said nucleic acid can inhibit the expression of the gene of human protein kinase C-α in a host cell in anti-sense orientation to a promoter.

11. (withdrawn) The method of claim 9, wherein said nucleic acid is selected from the group consisting of

a) a nucleic acid coding for human protein kinase C-α, or a fragment thereof;

b) a nucleic acid which is complementary to the nucleic acid of group a), or a fragment thereof;

c) a nucleic acid which is obtainable by substitution, addition, inversion and/or deletion of one or more bases of a nucleic acid of group a) or b), or a fragment thereof; and

d) a nucleic acid which has more than 80% homology with a nucleic acid any of group a) through c), or a fragment thereof.

12. (withdrawn) The method of claim 11, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 10 nucleotides.

13. (withdrawn) The method of claim 9, wherein said nucleic acid is a DNA or a RNA.

14. (withdrawn) The method of claim 9, wherein said nucleic acid or fragment thereof is inserted in a vector under the control of at least one expression regulating element in antisense orientation thereto.

15. (withdrawn) The method of claim 14, wherein said vector is selected from the group consisting of a plasmid, a cosmid, a bacteriophage or a virus.

16. (withdrawn) The method of claim 14, wherein said expression regulating element is selected from the group consisting of a promoter, a ribosome binding site, a signal sequence or a 3' transcription terminator.

17. (withdrawn) The method of claim 14, wherein said vector is contained in a host cell.

18. (withdrawn) The method of claim 17, wherein said host cell is a mammalian cell.

19. (withdrawn) The method of claim 9, wherein said substance which inhibits or reduces the expression of protein kinase C-α is an activator of protein kinase C-α.

20. (withdrawn) The method of claim 19, wherein said activator is a phorbol compound.

21. (withdrawn) The method of claim 20, wherein said phorbol compound is selected from a group consisting of 12-O-tetradecanoylphorbol-13-acetate (TPA) and phorbol-12,13-dibutyrate (PDBu).

22. (withdrawn) The method of claim 9, wherein said inhibitor of protein kinase C-α activity is an antibody which reacts with protein kinase C-α.

23. (withdrawn) The method of claim 22, wherein said antibody is selected from a group consisting of a monoclonal antibody and a polyclonal antibody.

24. (withdrawn) The method of claim 22, wherein said antibody is a humanized antibody.

25. (previously presented)The method of claim 9, wherein said inhibitor of protein kinase C-α activity changes the phosphorylation state of protein kinase C-α.

26. (previously presented)The method of claim 25, wherein said inhibitor is tocopherol.

27. (withdrawn) The method of claim 9, wherein said antagonist is selected from a group consisting of a derivative and an analogue of protein kinase C-α.

28. (currently amended) The method of claim 1, wherein ~~said agent which reduces or inhibits the expression and/or activity of~~ the inhibitor of protein kinase C-α is an agent which reduces or inhibits the expression and/or activity of protein kinase C-β.

29. (withdrawn) The method of claim 28, wherein said agent is cyclosporine A.

30. (currently amended) The method of claim 1, wherein ~~said agent which specifically reduces or inhibits the expression and/or activity of~~ the inhibitor of protein kinase C-α is administered in combination with an agent which reduces or inhibits the expression and/or activity of protein kinase C-β.

31. (previously presented) The method of claim 30, wherein said agent which reduces or inhibits the expression and/or activity of protein kinase C-β is selected from the group consisting of at least one nucleic acid which reduces or inhibits the expression of the protein kinase C-β gene, a vector containing said nucleic acid, a host cell containing said vector, a substance which reduces or inhibits the expression of protein kinase C-β, a substance which inhibits the translocation of protein kinase C-β, an antagonist of protein kinase C-β activity, and an inhibitor of protein kinase C-β activity.

32. (withdrawn) The method of claim 31, wherein said nucleic acid is selected from the group consisting of

a) a nucleic acid coding for human protein kinase C-β, or a fragment thereof;

b) a nucleic acid which is complementary to the nucleic acid of group a), or a fragment thereof;

c) a nucleic acid which is obtainable by substitution, addition, inversion and/or deletion of one or more bases of a nucleic acid of group a) or b), or a fragment thereof; and

d) a nucleic acid which has more than 80% homology with a nucleic acid of any of group a) through c), or a fragment thereof.

33. (withdrawn) The method of claim 32, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 10 nucleotides.

34. (withdrawn) The method of claim 31, wherein said nucleic acid is a DNA or a RNA.

35. (withdrawn) The method of claim 31, wherein said nucleic acid or fragment thereof is inserted in a vector under the control of at least one expression regulating element in antisense orientation thereto.

36. (withdrawn) The method of claim 35, wherein said vector is a plasmid, a cosmid, a bacteriophage or a virus.

37. (withdrawn) The method of claim 35, wherein said expression regulating element is a promoter, a ribosome binding site, a signal sequence or a 3' transcription terminator.

38. (withdrawn) The method of claim 35, wherein said vector is contained in a host cell.

39. (withdrawn) The method of claim 38, wherein said host cell is a mammalian cell.

40. (withdrawn) The method of claim 31, wherein said inhibitor of protein kinase C-β activity is an antibody which reacts with protein kinase C-β.

41. (withdrawn) The method of claim 40, wherein said antibody is a monoclonal or a polyclonal antibody.

42. (withdrawn) The method of claim 40, wherein said antibody is a humanized antibody.

43. (previously presented) The method of claim 31, wherein said inhibitor of protein kinase C-β activity changes the phosphorylation state of protein kinase C-β.

44. (withdrawn) The method of claim 31, wherein said antagonist is a derivative of protein kinase C-β or an analogue of protein kinase C-β.

45-55. (cancelled)

56. (withdrawn) The method of claim 11, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 50 nucleotides.

57. (withdrawn) The method of claim 11, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 200 nucleotides.

58. (withdrawn) The method of claim 18, wherein said host cell is a human cell.

59. (withdrawn) The method of claim 32, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 50 nucleotides.

60. (withdrawn) The method of claim 32, wherein said fragment of the nucleic acid of any of group a) through d) comprises at least 200 nucleotides.

61. (withdrawn) The method of claim 39, wherein said host cell is a human cell.

REMARKS

Introduction

Claims 1, 2, 9, 25-26, 28, 30-31, and 43 are pending and under examination. Claims 10-24, 27, 29, 32-42, 44, and 56-61 are pending but have been withdrawn. Claims 1, 28, and 29 have been amended. Support for these amendments can be found throughout the specification, for example, in the claims as filed and at paragraphs [0039], [0053], and [0056]. No new matter is believed to have been added.

Claims 3-8 and 45-55 are cancelled without prejudice to the subject matter therein. Applicant expressly reserves the right to pursue the subject matter of these claims in this application via rejoinder or in another application.

Rejections under 35 U.S.C. § 112

A. First Paragraph – Written Description

The Examiner has rejected claims 1-2, 9, 25-26, 28, 30-31, and 43 under the first paragraph of 35 U.S.C. § 112 as allegedly lacking sufficient written description. Applicants disagree. However, solely to expedite prosecution, claim 1 has been amended to recite the elected species "inhibitor of PKCα" as the Examiner suggested. The Examiner has not shown that one of skill in the art would recognize that Applicant was not in possession of the claimed invention.

The phrase "inhibitor of PKCα" has written description throughout the specification, for example, in the claims as filed and at paragraphs [0039], [0053], and [0056]. Applicant further exemplifies compounds belonging to this genus, such as, antisense oligonucleotides of the gene coding for PKCα, tocopherol, and phorbol compounds. See pg. 9, [0088].

Moreover, Applicant has also provided guidance on how to determine other members of the genus when Applicant states "'inhibitor' means a substance which competitively inhibits the

biological activity of protein kinase C-α, allosterically changes the spatial structure of PKC-α, or inhibits PKC-α by substrate inhibition." See pg. 6, paragraph [0056].

There is explicit written description support for the amended claims and sufficient guidance in the specification to allow persons of ordinary skill in the art to recognize that Applicant was in possession of what is claimed at the time of filing. Therefore, the amended claims have sufficient written description and this rejection is now believed to be moot. Its withdrawal is respectfully requested.

B. First Paragraph – Enablement

The Examiner has rejected claims 1-2, 9, 25-26, 28, 30-31, and 43 under the first paragraph of 35 U.S.C. § 112 as allegedly failing to comply with the enablement requirement. Applicants disagree. The basis for the Examiner finding a lack of enablement of the claims is not clear.

Moreover, Appendix A, which accompanies this response, contains data demonstrating that angiotensin-II does not significantly impair cardiac output in knock-out mice. Cardiac contractility in angiotensin-II treated wild type animals was significantly decreased, whereas in angiotensin-II treated knock-out mice contractility was nearly the same as in untreated wild-type or knock-out mice. This experimental data shows that PKCα is an important mediator of cardiac contractility and left ventricular hypertrophy. See page 4 of Appendix A, last sentence. Accordingly, the claimed methods of using inhibitors of PKCα are fully enabled for treating or preventing cardiovascular diseases. Applicant respectfully requests that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 1-2, 9, 25-26, 28, 30-31, and 43 under 35 U.S.C. § 102 as allegedly being inherently anticipated by U.S. Patent Number 5,871,766 issued to Hennekens (the '766 patent). The Examiner notes that the '766 patent is silent on the use of PKCα inhibiting

compounds but contends that such uses are inherently disclosed. It is respectfully submitted that the Examiner has not established inherent anticipation.

MPEP section 2112 states that the burden is on the Examiner to provide evidence of inherent anticipation. This MPEP section states that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities." Importantly, "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP section 2112, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

The Examiner has not shown evidence in the '766 patent that suggests the administration of an effective amount of a PKCα inhibitor to treat cardiovascular disease. The '766 patent purports to teach the use of Vitamin E and the biologically active analogs thereof to inhibit major vascular events. See col. 4, ll. 42-43. These analogs include "molecules which demonstrate equivalent biological function but which differ structurally . . . [and] include all other tocopherols." See col. 4, ll. 42-46. The '766 patent does not provide working examples of using Vitamin E in treating heart disease and instead provides an example of the use of beta-carotene and/or aspirin.

Moreover, as the Examiner notes, the '766 patent is silent on the use of an effective amount of **inhibitors of PKCα** to treat or prevent heart disease. It merely purports to disclose the use of vitamin E, a term that encompasses at least eight different enantimeric compositions for tocopherols and tocotrienoles, to inhibit vascular events. The '766 patent does not disclose which Vitamin E analogs are effective in treating heart disease nor provide any guidance on which may inhibit PKCα. There is insufficient evidence in the '766 patent to demonstrate the effectiveness of **inhibitors of PKCα**, including tocopherol, in methods of treating cardiovascular disease or for one of skill in the art to appreciate such a use for inhibitors of PKCα. Without more evidence, the current inherent anticipation rejection is improperly based on probabilities and possibilities and not the requisite extrinsic evidence. Therefore, Applicant respectfully requests that the rejection of the claimed genus of **inhibitors of PKCα** based upon the '766 patent be withdrawn.

In view of the above amendment and arguments, Applicant believes the pending application is in condition for allowance.

Dated: February 7, 2008

Respectfully submitted,

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